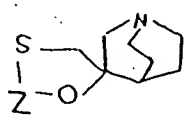
CLAIMS

1. Quinuclidine derivatives having the general formula (I)



and geometrical isomers, enantiomers, diastereoisomers, racemates and/or acid addition salts thereof, wherein Z represents the group $>CR^1R^2$ or two hydrogen atoms; R^1 is selected from the group consisting of hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl which is substituted by one or more aryl groups, and R^2 is selected from the group consisting of alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl which is substituted by one or more aryl groups.

2. Quinuclidine derivatives according to claim 1, wherein Z represents the group $>CR^1R^2$, R^1 is hydrogen, and R^2 is selected from the group consisting of alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl which is substituted by one or more aryl groups.

3. Quinuclidine derivatives according to claim 1, wherein Z represents the group $>CR^1R^2$, R^1 is selected from the group consisting of alkyl, cyclopentyl and cyclohexyl, and R^2 is selected from the group consisting of alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl which is substituted by one or more aryl groups.

4. Quinuclidine derivatives according to claim 1, wherein Z represents the group $>CR^1R^2$, R^1 is aryl, and R^2 is selected from the group consisting of aryl, diarylmethylol, and alkyl which is substituted by one or more aryl groups.

5. A quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is methyl.

6. A quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is phenyl.

7. A quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is diphenylmethyl.

8. A quinuclidine derivative as defined in claim 2, wherein of R^1 is hydrogen and R^2 is selected from the group consisting of ethyl, propyl, 1-pyrenepropyl and diphenylmethylol.

9. A quinuclidine derivative as defined in claim 3, wherein R^1 is methyl and R^2 is phenyl.

10. A quinuclidine derivative as defined in claim 3, wherein R^2 is phenyl and R^1 is selected from the group consisting of ethyl and cyclohexyl.

11. A quinuclidine derivative as defined in claim 4, wherein R^1 and R^2 are each phenyl.

12. A quinuclidine derivative as defined in claim 1, wherein Z represents two hydrogen atoms.

12. The geometrical isomer of the compound according to claim 5, the hydrochloric acid salt of which has the relatively lower melting-point (the cis-isomer).

13. The geometrical isomer of the compound according to claim 5, the hydrochloric acid salt of which has the relatively higher melting-point (the trans-isomer).

14. The hydrochloric acid salt of the compound according to claim 5.

15. The relatively lower melting-point geometrical isomer (the cis-isomer) of the compound according to claim 14.

16. The relatively higher melting-point geometrical isomer (the trans-isomer) of the compound according to claim 14.

18. A process for preparing quinuclidine derivatives according to claim 1, and wherein Z represents the group $>CR^1R^2$, which comprises reacting 3-hydroxy-3-mercaptomethylquinuclidine with a carbonyl compound of formula R^1-CO-R^2, and isolating the desired product from the reaction mixture.

19. A process according to claim 18, wherein the process is carried out in the presence of an acid catalyst.

20. A process according to claim 19, wherein the catalyst is a Lewis acid.

21. A process according to claim 20, wherein the Lewis acid is boron trifluoride.

22. A process for preparing quinuclidine derivatives according to claim 1, and wherein Z represents the group $>CR^1R^2$, which comprises reacting 3-hydroxy-3-mercaptomethylquinuclidine with a carbonyl compound of formula R^1-CO-R^2, in an atmosphere of nitrogen, at a temperature in the range of about 20 to about 30°C, in the presence of boron trifluoride etherate as catalyst and in a solvent medium which comprises one or more members selected from the group consisting of dichloromethane and chloroform, and isolating the desired product from the reaction mixture.

23. A process according to claim 22, wherein the reaction is effected at a temperature of about 25°C.

24. A process according to claim 22, wherein the reaction ingredients are first mixed in an atmosphere of nitrogen at a temperature between about -10 and +20°C, and the mixture thus obtained is permitted to rise to the reaction temperature.

25. A process according to claim 24, wherein the mixing temperature is about 0°C.

26. A process according to claim 18, further comprising isolating the desired product is separated into its geometrical isomers.

27. A process according to claim 26, wherein the separation is effected by fractional crystallization.

28. A process according to claim 18, wherein the product is isolated as the free base and thereafter converted to its acid addition salt.

29. A process according to claim 18, wherein the product is isolated in the form of an acid addition salt and thereafter converted to the free base.

30. A process according to claim 18, wherein the reaction is carried out in the presence of an inert organic solvent.

31. A process according to claim 30, wherein the inert organic solvent comprises one or more members selected from the group consisting of dichloromethane and chloroform.

32. A process for preparing the compound defined in claim 12, wherein the epoxide of 3-methylenequinuclidine is reacted with hydrogen sulfide.

33. A process according to claim 32, wherein the reaction is carried out in presence of a base.

34. A process according to claim 33, wherein the base is sodium hydroxide.

35. A process according to claim 33, wherein the reaction is carried out in an aqueous medium.

36. A process according to claim 32, wherein the said epoxide is prepared by reacting quinuclidin-3-one with dimethylsulfoxonium methylide.

37. A process according to claim 18, wherein the 3-hydroxy-3-mercaptomethylquinuclidine is prepared by reacting the epoxide of 3-methylenequinuclidine with hydrogen sulfide.

38. A process according to claim 37, wherein the reaction of epoxide with hydrogen sulfide is carried out in presence of a base.

39. A process according to claim 38, wherein the base is sodium hydroxide.

40. A process according to claim 38, wherein the reaction of epoxide with hydrogen sulfide is carried out in an aqueous medium.

41. A process according to claim 37, wherein the said epoxide is prepared by reacting quinuclidin-3-one with dimethylsulfoxonium methylide.

42. A pharmaceutical composition which comprises a quinuclidine derivative of formula (I) as defined in claim 1, and wherein Z represents the group $>CR^1R^2$, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

43. A pharmaceutical composition according to claim 42, which is in a form suitable for oral, rectal or parenteral administration, or for administration by insufflation.

44. A pharmaceutical composition according to claim 42, which is in a form suitable for transdermal administration.

~~45.~~ A pharmaceutical composition according to claim ~~42~~ 18, which is in unit dosage form.

46. A pharmaceutical composition for transdermal administration, which comprises a quinuclidine derivative of formula (I) as defined in claim 1, wherein Z represents the group $>CR^1R^2$, or a pharmaceutically compatible acid addition salt thereof, as well as a low molecular weight fatty acid.

~~47.~~ 22 A pharmaceutical composition according to claim ~~42~~ 17, wherein the ~~quinuclidine derivative~~ compound of formula (I) is that in which R^1 is phenyl, and R^2 is selected from the group consisting of ethyl, cyclohexyl and phenyl.

~~48.~~ 23 A pharmaceutical composition according to claim ~~42~~ 17, wherein the ~~quinuclidine derivative~~ compound of formula (I) is that in which R^1 is hydrogen, and R^2 is selected from the group consisting of methyl and ethyl.

~~49.~~ 24 A pharmaceutical composition according to claim ~~42~~ 17, wherein the ~~quinuclidine derivative~~ compound of formula (I) is that defined in claim ~~13.~~ 12

~~50.~~ 25 A pharmaceutical composition according to claim ~~49~~ 24, ~~which contains additionally~~ further comprising one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

51. A pharmaceutical composition according to claim 42, wherein the quinuclidine derivative of formula (I) is that in which R^2 is selected from the group consisting of alkyl containing three or more carbon atoms, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl, and R^1 is selected from the group consisting of hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl.

~~52.~~ 27 A pharmaceutical composition according to claim ~~51,~~ 26 wherein the ~~quinuclidine derivative~~ compound of formula (I) is that in which R^1 is methyl and R^2 is phenyl.

~~53.~~ 28 A pharmaceutical composition according to claim ~~51,~~ 26 wherein the ~~quinuclidine derivative~~ compound of formula (I) is that in which R^1 is hydrogen and R^2 is diphenylmethyl.

~~54.~~ 29 A pharmaceutical composition according to claim ~~51,~~ 26 wherein the ~~quinuclidine derivative~~ compound of formula (I) is that in which R^1 is hydrogen, and R^2 is selected from the group consisting of propyl, phenyl, ~~1-pyrenepropyl,~~ and diphenylmethylol.

55. A quinuclidine derivative as defined in claim 1 wherein Z represents the group $>CR^1R^2$, when prepared by the process of claim 18.

56. A quinuclidine derivative as defined in claim 12, when prepared by the process of claim 32.

57. A method for treating diseases of the central nervous system in mammals, which comprises administering to the mammal a quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, as defined in claim 1 wherein Z represents the group $>CR^1R^2$.

58. A method for treating diseases of the central nervous system in mammals, ~~which~~ comprising administering to the mammal a pharmaceutical composition according to ~~as defined~~ in claim 17.

59. A method for treating diseases of the central nervous system in mammals, which comprises transdermal administration to the mammal of a quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, as defined in claim 1 wherein Z represents the group $>CR^1R^2$.

60. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, which comprises administering to the mammal a quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is methyl, and including geometrical isomers, enantiomers, racemates and/or acid addition salts thereof.

61. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, which comprises administering to the mammal a pharmaceutical composition containing a quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is methyl, and including geometrical isomers, enantiomers, racemates and/or acid addition

salts thereof, together with an inert carrier or diluent.

62. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, which comprises transdermal administration to the mammal of a quinuclidine derivative as defined in claim 2, wherein R^1 is hydrogen and R^2 is methyl, and including geometrical isomers, enantiomers, racemates and/or acid addition salts thereof.

63. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, as defined in claim 1 wherein the quinuclidine derivative of formula (I) is that in which Z represents the group $>CR^1R^2$, R^2 is selected from the group consisting of alkyl containing three or more carbon atoms, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl, and R^1 is selected from the group consisting of hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl.

64. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a pharmaceutical composition containing a quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, as defined in claim 1 wherein Z represents the group $>CR^1R^2$, R^2 is selected from the group consisting of alkyl containing three or more carbon atoms, cyclopentyl, cyclohexyl,

aryl, diarylmethylol, and alkyl substituted by aryl, and R^1 is selected from the group consisting of hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl, together with an inert carrier or diluent.

65. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises transdermal administration to the mammal of a quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, as defined in claim 1 wherein Z represents the group $>CR^1R^2$, R^2 is selected from the group consisting of alkyl containing three or more carbon atoms, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl, and R^1 is selected from the group consisting of hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, and alkyl substituted by aryl.

66. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a quinuclidine derivative as defined in claim 7, or a pharmaceutically compatible acid addition salt thereof.

67. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a pharmaceutical composition containing a quinuclidine derivative as defined in claim 7, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

68. A method for treating or diseases due to a deficiency in the central cholinergic hyperfunction in mammals, which comprises transdermal administration to the mammal of a quinuclidine derivative as defined in claim 7, or a pharmaceutically compatible acid addition salt thereof.

69. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a quinuclidine derivative as defined in claim 9, or a pharmaceutically compatible acid addition salt thereof.

70. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises administering to the mammal a pharmaceutical composition containing a quinuclidine derivative as defined in claim 9, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

71. A method for treating diseases due to cholinergic hyperfunction in mammals, which comprises transdermal administration to the mammal of a quinuclidine derivative as defined in claim 9, or a pharmaceutically compatible acid addition salt thereof.

72. A method for treating senile dementia of Alzheimer's type, which comprises administering to a patient a quinuclidine derivative as defined in claim 13, or a pharmaceutically compatible acid addition salt thereof.

Claim 10

73. A method for treating senile dementia of Alzheimer's type, which comprises administering to a patient a pharmaceutical composition containing a quinuclidine derivative as defined in claim 13, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

74. A method for treating senile dementia of Alzheimer's type, which comprises transdermal administration to a patient of a quinuclidine derivative as defined in claim 13, or a pharmaceutically compatible acid addition salt thereof.

C 48 ~~75.~~ A method according to claim 45 ~~72~~ wherein there is coadministered with said compound ~~quinuclidine derivative,~~ one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

C 49 ~~76.~~ A method according to claim 46 ~~45~~ wherein there is coadministered with said compound ~~quinuclidine derivative~~, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

C 50 ~~77.~~ A method according to claim 47 ~~74~~ wherein there is coadministered with said compound ~~quinuclidine derivative,~~ one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, 4-aminopyridine and 3,4-diaminopyridine.

78. A process according to claim 32 wherein the reaction is carried out in the presence of an organic solvent medium.

79. A process according to claim 78 wherein the organic solvent medium comprises dimethyl sulfoxide.

80. A process according to claim 79 wherein the solvent medium comprises a member selected from the group consisting of chloroform and toluene.

81. A process according to claim 37 wherein the reaction of epoxide with hydrogen sulfide is carried out in the presence of an organic solvent medium.

82. A process according to claim 81 wherein the organic solvent medium comprises dimethyl sulfoxide.

83. A process according to claim 82 wherein the solvent medium comprises a member selected from the group consisting of chloroform and toluene.

84. A pharmaceutical composition which is in unit dosage form and which comprises a quinuclidine derivative of formula (I) as defined in claim 1, wherein Z represents the group $>CR^1R^2$, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 0.5 to about 500 mg., together with an inert carrier or diluent.

85. A pharmaceutical composition according to claim 84 and which comprises the said quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 5 to about 100 mg.

86. A pharmaceutical composition according to claim 85 and which comprises the said quinuclidine derivative, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 10 to about 50 mg.

87. A pharmaceutical composition according claim 84, wherein the quinuclidine derivative of formula (I) is that defined in claim 13.

88. A pharmaceutical composition according to claim 87, which contains additionally one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

89. A pharmaceutical composition according to claim 84, which is adapted for oral administration.

90. A pharmaceutical composition according to claim 84, which is adapted for parenteral administration.

91. A method for treating senile dementia of Alzheimer's type, which comprises administering to a patient via the oral route, a quinuclidine derivative as defined in claim 13, or a

pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 0.1 to about 60 mg./kg. body weight.

92. A method according to claim 91 wherein said amount ranges from about 0.5 to about 10 mg./kg. body weight.

93. A method according to claim 92 wherein said amount ranges from about 1 to about 5 mg./kg. body weight.

94. A method according to claim 91, wherein there is coadministered with the said compound one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

95. A method according claim 91, wherein administration is by means of a pharmaceutical composition in unit dosage form which contains the said quinuclidine derivative in an amount in the range of about 0.5 to about 500 mg., together with an inert carrier or diluent.

96. A method for treating senile dementia of Alzheimer's type, which comprises administering to a patient via the parenteral route, a quinuclidine derivative as defined in claim 13, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 0.01 to about 40 mg./kg. body weight.

97. A method according to claim 96 wherein said amount lies in the range of about 0.05 to about 5 mg./kg. body weight.

98. A method according to claim 97 wherein said amount lies in the range of about 0.1 to about 2 mg./kg. body weight.

99. A method according to claim 96, wherein there is also coadministered with the said quinuclidine, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

100. A method according to claim 96, wherein administration is by means of a pharmaceutical composition in unit dosage form which contains the said quinuclidine derivative in an amount in the range of about 0.5 to about 500 mg., together with an inert carrier or diluent.